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Effect of Rapamycin on Renal Ischemia Reperfusion Injury

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Background: The aim of this study was to determine the effect of rapamycin (Rapa), a relatively new immunosuppressive drug, on renal ischemia reperfusion injury (IRI) in the mouse. **Methods:** Renal IRI was induced in male Balb/c mice by clamping both renal pedicles for 45 minutes. The mice were treated with either vehicle or Rapa (2 mg/kg/day) by oral gavage, starting 2 days before the IRI and continued daily until sacrifice. The mice were sacrificed at 1, 3, and 7 days after the operation. The severity of the IRI was assessed by serum creatinine levels and renal histology. Proliferation of renal tubular cells was quantified by immunohistochemical staining for proliferating cell nuclear antigen (PCNA). **Results:** One day after the IRI, the serum creatinine levels of Rapa-treated mice were significantly higher than those of vehicle-treated mice. Kidney sections from Rapa-treated mice also showed more marked tubular damage on day 1. The number of PCNA-positive cells in Rapa-treated mice was significantly lower than that in vehicle-treated mice on days 1 and 3 after IRI. By day 7 after IRI, there was no significant difference between Rapa- and vehicle-treated mice in terms of serum creatinine levels, renal histology and positive PCNA staining.

	Serum creatinine (μmol/L)			PCNA + nuclei/microscopic field		
	Vehicle	Rapa	*p*	Vehicle	Rapa	*p*
Day 1	19.8 ± 6.3	26.8 ± 4.8	0.037	13.5 ± 4.9	1.6 ± 0.7	< 0.005
Day 3	16.0 ± 4.0	16.4 ± 2.4	0.72	12.5 ± 7.0	1.1 ± 1.1	0.01
Day 7	14.6 ± 3.0	15.0 ± 2.1	0.47	8.2 ± 3.1	9.3 ± 2.5	0.87

Conclusion: We conclude that Rapa treatment aggravates renal IRI during the first 1 to 3 days after the insult. This effect might be partly mediated through inhibition of renal tubular cell regeneration.

The Relationship Between β1-adrenergic Receptor Polymorphisms and Cardiovascular Disease in Peritoneal Dialysis Patients

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Background: Recent studies show that a common gain-of-function polymorphism of β1-adrenergic receptor (389 Gly→Arg) plays an important role in the pathogenesis of hypertension and heart failure in patients with normal renal function. We studied the relationship between β1-adrenergic receptor polymorphism and cardiovascular disease in peritoneal dialysis (PD) patients. **Methods:** We studied 189 new PD patients. The β1-adrenergic receptor genotype was determined by polymerase chain reaction–restriction fragment length polymorphism assay. They were then prospectively followed for the development of cardiovascular events. All-cause mortality and duration of hospitalization for cardiovascular diseases were also recorded. **Results:** There were 95 male cases. The mean age was 56.2 ± 14.8 years. Eighty-six patients (45.5%) were diabetic; 81 (42.9%) received beta-blocker therapy. Only one case was homozygous for the mutant CC genotype. The prevalence of GG, GC, and CC genotypes were 34.9%, 64.6%, and 0.5% respectively. There was no difference in the prevalence of pre-existing cardiovascular disease between genotype groups. For GG and GC/CC genotypes, actuarial patient survival was 80.2% and 85.1% at 24 months, respectively ($p = 0.53$); event-free survival was 63.6% and 71.5% at 24 months, respectively ($p = 0.26$); and the duration of hospitalization was 15.9 ± 3.0 and 16.6 ± 2.3 days per year, respectively ($p = 0.8$). The result remained similar when patients with and without beta-blocker treatment were separately analyzed. **Conclusion:** Our study demonstrates that the β1-adrenergic receptor (389 Gly→Arg) polymorphism is not related to cardiovascular disease in PD patients. Nevertheless, the low prevalence of the mutant CC genotype in new PD patients suggests either that this genotype is protective for renal failure or that these patients have high mortality before they progress to dialysis-dependent renal failure.

Role of PPAR-γ Agonist in Diabetic Nephropathy: An *In Vitro* Study

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Background: We have previously shown that advanced glycation end products (AGEs) in the form of glycated bovine serum albumin (gBSA) incite a proinflammatory phenotype in proximal tubular epithelial cells (PTECs). Emerging data suggest that peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists may possess anti-inflammatory properties in addition to their insulin-sensitizing effect in diabetes. **Methods:** We investigated the intracellular signal transduction mechanism of gBSA and the impact of the PPAR-γ agonist in an *in vitro* model of diabetic tubulopathy. Human PTECs, obtained from primary culture, were exposed to medium alone, or supplemented with BSA (0.5 mg/mL) or gBSA (0.5 mg/mL) with or without prior addition of rosiglitazone (0.1–0.5 μM). **Results:** Exposure to gBSA, but not BSA, significantly upregulated both mRNA gene and protein expression of IL-8 ($p = 0.009$ and $p < 0.001$ vs BSA, respectively) and sICAM-1 ($p = 0.017$ and $p = 0.05$ vs BSA, respectively), which were dose-dependently attenuated by rosiglitazone. Also in a dose-dependent fashion, gBSA, but not BSA, caused nuclear translocation of nuclear factor-kappa B (NF-κB) and activation of mitogen-activated protein kinases (MAPK) p44 and p42. Both NF-κB and MAPK signals were unaffected by concurrent treatment with rosiglitazone. **Conclusion:** AGEs potentiate tubular inflammation that may be modified by PPAR-γ ligation independent of NF-κB transcriptional activity and MAPK signaling. The anti-inflammatory effects of PPAR-γ agonists in diabetic nephropathy may lie downstream to NF-κB and MAPK pathways.

Antibody Response to Hepatitis B Vaccine in End-stage Renal Disease Patients

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Background: This retrospective and comparative study evaluated the relationship between different factors which may contribute to suboptimal immunologic response to intramuscular recombinant hepatitis B vaccine in end-stage renal disease subjects. **Methods:** From a cohort of 64 dialysis subjects undergoing primary vaccination with Engerix-B, we determined the predictive factors that impinged on patients' response to vaccine, as defined by anti-HBs level ≥ 10 mIU/L. Dose efficacy was further evaluated by comparing three historical cohorts vaccinated with the regimens of 20 μg, 40 μg and 80 μg per dose respectively. **Results:** We identified 64 end-stage renal disease patients (mean age, 43 ± 12 years; 81% receiving peritoneal dialysis) who received primary vaccination from April 1997 to September 2004. Median follow-up was 6.5 years. They achieved a seroconversion rate of 81%. Older age, diabetes mellitus, obesity and low Engerix-B dose were risk factors of inadequate anti-HBs response by univariate analysis. By stepwise logistic regression analysis, hepatitis B vaccine dose was the only independent predictive factor of impaired antibody response. An Engerix-B vaccine dose of 20 μg was associated with a more than tenfold increase in risk of non-response to hepatitis B vaccine (hazards ratio, 32.2; 95% CI, 3.85–250.0). Immunization with 80 μg of Engerix-B increased the likelihood of persistent protective antibody (log-rank test, $p = 0.014$). Immunization with Engerix-B 80 μg is estimated to prevent one extra end-stage renal disease subject who would lose seroprotective anti-HBs level at 1 year for every 5.6 patients treated (number needed to treat to benefit, 5.6; 95% CI, 5.4–5.8]). **Conclusion:** Our results suggest the potential for the three-dose schedule of recombinant vaccine Engerix-B 80 μg to prolong the immune response among end-stage renal disease patients.